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Date: Sat, 26 Apr 2003 20:45:40 -0700
Content-Type: text/plain

RSRFNewsAlert
 April 27, 2003

The latest issue of the RSRFlash has been mailed to everyone on the RSRF mailing list. It's available online at <http://www.rsr.org/newsletter.shtml>

Two exciting fundraising events will take place on May 18th: The First Annual Chefs' Classic 5-Miler & Celebration of Food in Sharon, MA and the Inaugural CT/NY/NJ Strollathon in Stamford, CT. For more information on both events please visit http://www.rsr.org/fundraising_events.shtml

Thinking about organizing a Strollathon fundraiser in your community? Let us know and we'll mail you our "How To Manual". Please email monica@rsrf.org

New Publications:

- * Study of MECP2 gene in Rett syndrome variants and autistic girls.
- * Rapid Genotyping of Common MeCP2 Mutations with an Electronic DNA Microchip Using Serial Differential Hybridization.

Interesting Developments:

- * Molecular machine shuffles beads on a DNA string
- * Is epilepsy an autoimmune disorder?
- * Nanotechnology may help overcome current limitations of gene therapy
- * Human Genome Project Completed

Stem Cell News:

- * Stem Cells May Repair Damage From MS
- * StemCells, Inc. Presents Preclinical Proof Of Concept For Treatment Of Batten Disease, A Fatal Neurological Disorder
- * Adult stem cells shown to develop into all brain cell types

Am J Med Genet 2003 May 15;119B(1):102-7

Study of MECP2 gene in Rett syndrome variants and autistic girls.

Zappella M, Meloni I, Longo I, Canitano R, Hayek G, Rosaia L, Mari F, Renieri A.

Department of Child Neuropsychiatry, Azienda Ospedaliera Senese, Siena, Italy.

Mutations in MECP2 gene account for approximately 80% of cases of Rett syndrome (RTT), an X-linked severe developmental disorder affecting young girls, as well as for most cases of Preserved Speech Variant (PSV), a mild RTT variant in which autistic behavior is common. The aim of this study is to determine whether MECP2 mutations are responsible for PSV only or may cause other forms of autistic disorders. We screened for mutations by SSCP 19 girls with a clinical diagnosis of autism, two of them fulfilling the PSV criteria. A pathogenic mutation was found only in the latter two cases (R133C and R453X). A long follow-up of these two girls revealed a unique clinical course. They initially developed the first three stages of RTT, they were severely retarded and had autistic behavior. Over the years their abilities increased progressively and by early adolescence they lost autistic behavior, becoming adequately accustomed to people and reaching an IQ close to 45. These results confirm previous clinical studies suggesting that a wide spectrum of RTT exists including girls with mental abilities considerably higher than in classic RTT. We conclude that MECP2 mutations (missense or late truncating) can be found in girls with an IQ close to 45 and a clinical history of PSV of Rett syndrome. Furthermore, MECP2 mutations are not found in patients in which autism remains stable over the years. Copyright 2003 Wiley-Liss, Inc.

PMID: 12707946 [PubMed - in process]

J Mol Diagn 2003 May;5(2):121-6

Rapid Genotyping of Common MeCP2 Mutations with an Electronic DNA Microchip Using Serial Differential Hybridization.

Thistlethwaite WA, Moses LM, Hoffbuhr KC, Devaney JM, Hoffman EP.

Research Center for Genetic Medicine, Children's National Medical Center, Washington, District of Columbia.

Rett syndrome is a neurodevelopmental disorder that affects females almost exclusively, and in which eight common point mutations on the X-linked MeCP2 gene are known to cause over 70% of mutation-positive cases. We explored the use of a novel platform to detect the eight common mutations in Rett syndrome patients to expedite and simplify the process of identification of known genotypes. The Nanogen workstation consists of a two-color assay based on electric hybridization and thermal discrimination, all performed on an electronically active NanoChip. This genotyping platform was tested on 362 samples of a pre-determined genotype, which had been previously identified by a combination of DHPLC (denaturing high performance liquid chromatography) and direct sequencing. This genotyping technique proved to be rapid, facile, and displayed a specificity of 100% with 3% ambiguity. In addition, we present consecutive testing of seven mutations on a single pad of the NanoChip. This was accomplished by tagging down two amplimers together and serially hybridizing for seven different loci, allowing us to genotype samples for seven of the eight common Rett mutations on a single pad. This novel method displayed the same level of specificity and accuracy as the single amplimer reactions, and proved to be faster and more economical.

PMID: 12707377 [PubMed - in process]

Molecular machine shuffles beads on a DNA string

Yards of DNA are packed into cells by wrapping the DNA around proteins called nucleosomes. But that tight packing makes it hard for the cell's machinery to get at the DNA code to read, copy or repair it. Now researchers at the University of California, Davis, have shown how two proteins form a molecular machine that shuffles the nucleosomes out of the way to expose the DNA double helix.

Postgraduate researchers Andrei Alexeev and Alexander Mazin, with Stephen Kowalczykowski, a professor of microbiology at UC Davis, studied a protein called Rad54 in brewer's yeast (*Saccharomyces cerevisiae*). Rad54 is known to bind to and change the shape of DNA strands.

Using a piece of DNA with artificial nucleosomes attached, the researchers found that Rad54 could not only move the nucleosomes along the strand but knock them off altogether.

When another protein, Rad51, was added, the process became much more efficient. Rad51 binds to single strands of DNA.

Together, Rad54 and Rad51 form a molecular machine that can carry a piece of DNA to the right place, push the nucleosomes out of the way, expose the DNA double helix and begin the process of stitching a new piece of DNA into place.

The work is published in the March issue of Nature Structural Biology.

Is epilepsy an autoimmune disorder?

15 April 2003 15:00 GMT

by Laura Spinney

A disease of the central nervous system with symptoms that include memory loss and seizures is caused by the body producing antibodies against a key brain protein, British researchers report. They have found low levels of the same antibodies in some patients with intractable epilepsy - evidence which, combined with a large new study soon to be published, could strengthen the case for viewing some forms of epilepsy as autoimmune disorders.

Angela Vincent, an immunologist in the neurosciences group at the Weatherall Institute of Molecular Medicine in Oxford, and her colleagues tested the blood of ten patients suffering from the rare condition limbic encephalitis (LE), and found that nine of them were carrying antibodies against the protein that forms voltage-gated potassium channels (VGKC) in the neuronal membrane-ion channels crucial to the cell's normal functioning.

They went on to show that immunotherapies that reduced the VGKC antibody count in these patients also produced an improvement in their symptoms, suggesting the antibodies play a causal role in the disease.

Vincent believes that LE is an autoimmune disease that may or may not be triggered by an initial viral infection that has cleared up.

Because some epilepsy syndromes are related to genetic defects in ion channels, she wondered if a similar immune mechanism might give rise to epilepsy or epilepsy-like symptoms, by attacking those same ion channels. So she and her colleagues also tested 115 adults with drug-resistant epilepsy for antibodies to VGKC.

Nine subjects tested positive, although with low concentrations; eleven were found to be carrying antibodies to an intracellular enzyme called glutamic acid decarboxylase (GAD).

To demonstrate that VGKC antibodies are playing a pathogenic role in those nine cases, says Vincent, they would have to show that they bind to the extracellular domain of the VGKC, rather than the intracellular domain, something she is now testing.>

"We know that in some conditions you get antibodies to the inside of the VGKC, but those antibodies are usually secondary to damage and are not the primary cause," she told BioMedNet News.

Similarly, the antibodies to GAD, which is found inside the cell, are probably an effect rather than a cause of epilepsy-related brain damage.

But, she added, if the antibodies do turn out to bind to the outside of the VGKC, "One would seriously think of trying to treat some of those patients with steroids or other immune treatments."

Edward Cooper, a neurologist at University of Pennsylvania Medical Center in Philadelphia, says these are "very exciting and potentially quite important findings," although it is too early to draw any firm conclusions from them.

"An autoimmune mechanism for refractory epilepsy is especially intriguing because of the mysterious latent period that is a feature in many cases," he said.

Epilepsy can occur transiently in childhood, then recur after a period of remission in adolescence or adulthood.

"Slow autoimmune attack on brain channels might contribute to this common natural history in some patients," Cooper speculated.

But Mia Levite, a neurobiologist at the Weizmann Institute of Science in Rehovot, Israel and Tel Aviv University who first coined the phrase "autoimmune epilepsy," points out that this is the first time potassium channels have been implicated in the disease and that they don't seem to be the major players.

"The focus now is primarily on antibodies to the glutamate receptor of the AMPA ionotropic subtype 3," she said.

Levite's team is about to publish a large-scale study in which they have attempted to correlate different types of epilepsy with different types and concentrations of antibodies in patients' blood and cerebrospinal fluid.

The results are "solid" regarding these glutamate receptors, she hints, adding that, once they are published, clinicians will be forced to reassess their diagnostic and therapeutic strategies to allow for an autoimmune component in epilepsy. But she warns that direct evidence that antibodies by themselves can cause epilepsy is still lacking.L

Vincent presented her work on April 14 at a meeting of the British Neuroscience Association in Harrogate, UK.

Nanotechnology may help overcome current limitations of gene therapy

Scientists from Northwestern University and Argonne National Laboratory have created a hybrid "nanodevice" composed of a "scaffolding" of titanium oxide nanocrystals attached with snippets of DNA that may one day be used to target defective genes that play a role in cancer, neurological disease and other conditions.

The titanium oxide nanocrystals, which are less than a few billionths of a meter in diameter and are the same material used in artificial hips and knees, may provide the ideal means of overcoming current limitations of gene therapy, such as adverse reactions to genetically modified viruses used as vehicles to deliver genes into cells, according to researchers Tatjana Paunesku and Gayle Woloschak of Northwestern University.

Paunesku is research assistant professor of radiology, and Woloschak is professor of radiology at the Feinberg School of Medicine at Northwestern University. They are both researchers at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University and at Argonne National Laboratory.

In experiments described in the May online version of Nature Materials, the research team showed that nanocomposites not only retain the individual physical and biological activity of titanium oxide and of DNA, but, importantly, also possess the unique property of separating when exposed to light or x-rays.

For example, researchers would attach to the titanium oxide scaffolding a strand of DNA that matches a defective gene within a cell and introduce the nanoparticle into the nucleus of the cell, where the DNA would bind with its "evil twin" DNA strand to form a double-helix molecule.

The scientists would then expose the nanoparticle to light or x-rays, which would snip off the defective gene. "We call it a 'Swiss army knife' because, unlike today's drugs, we can inject 10 kinds of good genes all at once and target them in extremely specific or extremely broad ways," Paunesku said.

The titanium oxide "scaffolding" also is amenable to attaching other molecules, for example, navigational peptides, or proteins, which, like viral vectors, can help the nanoparticles home in on the cell nucleus.

The research group's work is still in the early stages of development, and testing in a laboratory model is at least two years away, Woloschak said.

Also working on this project were Natasa Stojicevic, of the Feinberg School, and Tijana Rajh, Marion Thurnauer, Jorg Maser, Stefan Vogt, Gary Wiederrect, Miroslava Protic, Barry Lai and Jeremy Oryhon of Argonne National Laboratory.

Human Genome Project Completed
Laurie Barclay, MD

April 16, 2003 – Editor's Note: On April 14, the International Human Genome Sequencing Consortium announced the successful completion of the Human Genome Project, two and a half years ahead of schedule and \$0.3 billion under budget. Although an earlier draft of the genome sequence was revealed in June 2000, this update sequences the 3 billion DNA letters in the human genome with 99.99% accuracy and with fewer than 400 gaps in structure, representing less than 1.0% of the human genome's gene-containing regions.

"The Human Genome Project has been an amazing adventure into ourselves, to understand our own DNA instruction book, the shared inheritance of all humankind," Francis S. Collins, MD, PhD, director of the National Human Genome Research Institute (NHGRI) and leader of the Human Genome Project since 1993, says in a news release. "All of the project's goals have been completed successfully – well in advance of the original deadline and for a cost substantially less than the original estimates."

The International Human Genome Sequencing Consortium includes hundreds of scientists at 20 sequencing centers in China, France, Germany, Great Britain, Japan, and the U.S. The five institutions that sequenced the most portions of the human genome were Baylor College of Medicine in Houston, Texas; Washington University School of Medicine in St. Louis, Missouri; Whitehead Institute/MIT Center for Genome Research in Cambridge, Massachusetts; Department of Energy (DOE)'s Joint Genome Institute in Walnut Creek, California; and The Wellcome Trust Sanger Institute near Cambridge, England, which alone generated about 30% of the entire sequence.

Bonus spinoffs from the project, also delivered with startling speed, include an advanced draft of the mouse genome sequence released in December 2002; an initial draft of the rat genome sequence in November 2002; identification of more than 3 million human single nucleotide polymorphisms (SNPs); and the generation of full-length complementary DNAs (cDNAs) for more than 70% of known human and mouse genes. All of this sequence data resides in public databases, where it is freely available to scientists around the world, without restrictions on its use or redistribution.

Despite these landmark achievements, the NHGRI and the DOE, which led the U.S. portion of the international effort, believe that the real work has only just begun. NHGRI will set forth its revolutionary vision for the future of genomic research in the April 24 issue of Nature, remarkably coinciding with the 50th anniversary of Nature's publication of DNA's double helix structure as described by James Watson and Francis Crick.

"Never would I have dreamed in 1953 that my scientific life would encompass the path from DNA's double helix to the 3 billion steps of the human genome. But when the opportunity arose to sequence the human genome, I knew it was something that could be done – and that must be done," says Nobel Laureate James D. Watson, PhD, now president of Cold Spring Harbor Laboratory in Cold Spring Harbor, N.Y. "The completion of the Human Genome Project is a truly momentous occasion for every human being around the globe."

Now that the overall sequencing is complete, one of the next steps is to compare genetic differences among individuals and identify those associated with a specific condition, uncovering the genetic contributions to many diseases. Begun in October 2002 and slated for completion in three years, the International HapMap Project of NHGRI and its collaborators hope to produce the "next-generation" map of the human genome, identifying genes related to asthma, cancer, diabetes, heart disease, and other chronic conditions.

But has genome sequencing opened a Pandora's box of futuristic fears? To address these concerns, the Human Genome Project has devoted a significant portion of its budget to study the ethical, legal, and social implications of this research. NHGRI and DOE have also dedicated 3% to 5% of their genome budgets to examining how the exponential increase in human genetic knowledge may affect individuals, institutions, and society. Based on this work, more than 40 U.S. states have passed genetic nondiscrimination bills.

"Achieving the goals of the Human Genome Project is a historic milestone. But this is no time to rest and relax," Dr. Collins says. "With this foundation of knowledge firmly in place, the medical advances promised from the project can now be significantly accelerated."

Stem Cells May Repair Damage From MS

Wed Apr 16, 6:00 PM ET

By ALEX DOMINGUEZ, Associated Press Writer

Raising hopes of a treatment for multiple sclerosis, researchers have found that stem cells injected into mice can repair damage and sharply reduce symptoms from an experimental form of MS.

Seven of 26 mice recovered completely from hind-leg paralysis and others showed substantial improvement after the stem cells were injected into their spinal cords or blood.

The study's authors, from the San Raffaele Scientific Institute in Milan, Italy, say they now plan to try the procedure on monkeys using human stem cells, but caution that a treatment for human patients, if possible, is years away.

Multiple sclerosis occurs because the body mistakenly attacks the fatty substance that surrounds nerve fibers, interfering with signals sent by the brain. Symptoms can include slurred speech, numbness, blurred vision and muscle weakness, spasticity or paralysis.

About 400,000 Americans, mostly women, have MS, and most are diagnosed between the ages of 20 and 50, according the National Multiple Sclerosis Society. Current therapies help slow the disease by quieting the immune system attack on nerves, but no cure is known.

Researchers from the San Raffaele institute created a disease in the mice that mimics MS. In the experiment, the researchers used stem cells that had been removed from the brains of adult mice and grown into larger quantities in a laboratory.

Once injected, the cells traveled to damaged nerve areas and changed into cells needed to make repairs, according to the study published in Thursday's issue of the journal Nature.

Research on monkeys is expected to begin in the next few months, and the results are expected by the end of 2004, said Gianvito Martino, one of the study's authors.

"This opens new hope for patients, but the way is very long and very hard," Martino said. "We have seen the phenomenon, but now we have to dissect why we have seen this phenomenon and take all the steps to understand that."

The research raises the hope of reversing the damage caused by the disease, but does not address the cause, said Stephen Reingold, the MS society's vice president for research.

One impressive aspect of the approach is that the cells seem to seek out the damaged areas themselves, which is important because MS affects the entire central nervous system, Reingold said.

"This doesn't tell us it's going to work in humans, but at least it's a step forward," Reingold said.

If the work does eventually proceed to experiments with people, human fetal cells are most likely to be used, said Angelo Vescovi, one of the study's authors. Such cells will be used in the monkey study.

Vescovi said laboratory populations of such cells can be established with tissue from spontaneous miscarriages. Tissue matching will probably keep the recipient's body from rejecting them as foreign, Vescovi said.

Dr. Lawrence Steinman, a Stanford University neurologist, said overcoming rejection might not be easy because MS is an autoimmune disorder in which the body is already attacking its own tissue.

"I think a huge amount of research has to be done to figure out the conditions to do this in humans, to grow the types of cells that work so splendidly in mice," Steinman said.

"You have to have a way of shutting off the autoimmune disease if the process is ever going to work," he said. "On top of that, if they (the injected cells) are recognized as foreign, the immune system will also attack."

StemCells, Inc. Presents Preclinical Proof Of Concept For Treatment Of Batten Disease, A Fatal Neurological Disorder

4/11/2003

Source: StemCells, Inc.

StemCells, Inc. (STEM) will present preclinical data from a transplant study using the Company's proprietary human neural stem cells (CNS-SC) in Neuronal Ceroid Lipofuscinosis, a lysosomal storage disease commonly referred to as Batten Disease or NCL. Many lysosomal storage diseases, which include Tay-Sachs, Hunter, Krabbe, and Niemann-Pick diseases among others, are genetic disorders primarily affecting the central nervous system, in which enzyme deficiency causes the buildup of toxic waste materials. This results in the

eventual destruction of nerve cells leading to the symptomatology of the disease, seizures, blindness, loss of motor skills and premature death.

Nobuko Uchida, Ph.D., Director of the Company's Neural Program will present the data today at the 9th International Congress on NCL in Chicago showing widespread engraftment in mice designed to model Batten Disease, and persistent production of the enzyme that is deficient in this disease. Significantly, the study showed a measurable reduction in the toxic waste material as well as preliminary indications that neuronal loss is also retarded. The study was done at StemCells, Inc. and at the laboratory of Dr. William Mobley at Stanford University.

"'Batten disease' refers to several closely related genetic disorders caused by deficiency of an enzyme required for normal cell metabolism. This results in an abnormal buildup of waste substances -- cellular debris, so to speak -- inside the cells of the brain, eye and other tissues, that eventually leads to cell death. Batten disease primarily affects infants and young children," explained Dr. Stan Tamaki, Director of Monoclonal Antibody Discovery and co-director of the program. The transgenic mice used in the study reported today were engineered to delete the gene involved in the infantile form of Batten disease, so that the toxic substances build up in their brain, as they do in human patients. StemCells' purified banked human CNS-SC were transplanted into the mice, migrated throughout their brains, and produced cells that made the missing enzyme.

"We observed a statistically significant decrease in the amount of stored toxic waste material in the transplanted mice," said Dr. Ann Tsukamoto, Vice President of Research and Development, "and preliminary data also suggest that there is a larger number of surviving neurons in the brains of the transplanted transgenic mice compared to their non-transplanted littermates. We are delighted with these results. The improved neuronal survival needs to be confirmed with additional experiments, but these results give us hope that transplantation of our human CNS-SC may slow progression of or cure the disease. This has been a long time in coming. The mice had to be bred, tested for the mutation, and transplanted with the human cells, and then we had to wait an adequate time to insure long-term stability of the transplant. But it has been well worth the wait. Though good science in animal models takes a long time, it is the only way to insure true proof of concept for cell based therapies. Batten Disease is rare, but it is a debilitating condition that is fatal. There is no treatment currently available except palliative treatment to control some of the symptoms in the short run. It is our hope that our results will not only prove useful in Batten's, but can be extended to other lysosomal storage diseases that affect the central nervous system."

"There is a very large unmet need for new treatments for neurological disorders. StemCells, Inc. is successfully carrying out the proof of concept studies needed to develop treatments for the lysosomal storage disorders, diseases that disable and kill adults and children and for which current treatments are ineffective. There is genuine promise in the use of stem cells to treat and even cure these disorders," said Dr. William Mobley, Chairman Department of Neurology, Stanford University.

Phil Milto, President of the Nathan's Battle Foundation for Late Infantile NCL Therapy Development, stated "StemCells Inc.'s recent data is the most promising cell mediated data I have seen. These results are extremely encouraging for Batten's disease and potentially for all neurodegenerative disorders. The wide spread engraftment, large area of cell migration, and duration of enzyme production from their cells

strongly demonstrates the current viability for the development of therapies for neurodegenerative disorders using StemCells' technology. This is the type of data that therapy development groups like ours have dreamed of seeing!"

StemCells continues its work using its proprietary human CNS-SC in other areas of disease and disability. The Company previously announced the promising results of a pilot study evaluating the use of these cells in a preclinical stroke model, which were presented at the Society for Neuroscience 32nd Annual Meeting in Orlando, Florida on November 6; that study was performed at the Departments of Neurosurgery and Neurology at Stanford University under the direction of Gary Steinberg, M.D., Ph.D., Chairman Department of Neurosurgery; Co-Director, Stanford Stroke Center. Preclinical studies using the human CNS-SC in spinal cord injury is also ongoing.

Adult stem cells shown to develop into all brain cell types

MINNEAPOLIS/ST. PAUL (April 25, 2003) Researchers at the University of Minnesota provide evidence for the first time that stem cells derived from adult bone marrow and injected into the blastocyst of a mouse can differentiate into all major types of cells found in the brain. The results of the research are published as the lead article in the April 25, 2003 issue of Cell Transplantation. The potential of these adult stem cells, termed multipotent adult progenitor cells (MAPCs), were the subject of research reported in Nature in June 2002. The research reported this week in Cell Transplantation takes a specific look at the ability of MAPCs to develop into cells typically found in the brain.

Adult stem cells were injected into a mouse blastocyst, an early embryonic stage of a mouse. The result is the birth of a chimerical animal an animal that shows the presence of both the cells from the host mouse as well as cells that have developed from the transplanted stem cells. Within the brain, the transplanted stem cells developed into nerve cells that typically conduct electrical impulses, glial cells that provide support to the nerve cells, and myelin-forming cells that enhance the conduction of electrical impulses by nerve cells.

"This research takes our findings a step further," said principal investigator Walter C. Low, Ph.D., department of Neurosurgery, University of Minnesota Medical School.

Researchers looked at the specific phenotypes of the cells in the brain and found stem cell produced nerve cells in regions of the brain that undergo degeneration with Parkinson's disease, multiple sclerosis, Huntington's disease, ataxia, and Alzheimer's disease.

"This tells us that these adult stem cells are capable of becoming nerve cells that communicate with other nerve cells within the brain and form proper neural circuits that permit the chimerical mice to function normally," said co-investigator Catherine Verfaillie, M.D., director of the Stem Cell Institute at the University of Minnesota.

"The next step is to test what happens when the adult stem cells are used to treat mice and rats with neurological disorders," said lead author Dirk Keene, an M.D./Ph.D. student at the University of Minnesota

Medical School.

Researchers expect answers to that question within the year. Xilma Ortiz-Gonzalez, Yuehua Jiang, and David Largeaspada were co-authors on this study.

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